

emerged as a major complication of bortezomib therapy, which usually appears in the first courses of therapy with a number of sensory and painful symptoms, including reduced threshold to mechanical and cold stimuli. No satisfactory explanation or effective treatment exists for bortezomib-evoked CIPN.

Patients (or Materials) and Methods: In this study, we evaluated whether TRPA1 acted as a critical mediator of CIPN by bortezomib or oxaliplatin in a mouse model system.

Results: Our data demonstrated that CIPN hypersensitivity phenotype that was stably established by bortezomib could be transiently reverted by systemic or local treatment with the TRPA1 antagonist HC-030031. A similar effect was produced by the oxidative stress scavenger α -lipoic acid. Notably, the CIPN phenotype was abolished completely in mice that were genetically deficient in TRPA1, highlighting its essential role. Administration of bortezomib or oxaliplatin, which also elicits TRPA1-dependent hypersensitivity, produced a rapid, transient increase in plasma of carboxy-methyllysine, a by-product of oxidative stress. Short-term systemic treatment with either HC-030031 or α -lipoic acid could completely prevent hypersensitivity if administered before the cytotoxic drug.

Conclusion: Our findings highlight a key role for early activation/sensitization of TRPA1 by oxidative stress by-products in producing CIPN. Furthermore, they suggest prevention strategies for CIPN in patients through the use of early, short-term treatments with TRPA1 antagonists.

Disclosure of Interest: None declared.

PP272—MIGRAINE AND PARTHENOLIDE INHIBITION OF TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1

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Introduction: *Tanacetum parthenium* L. (feverfew) has long been known as a migraine remedy and, according to positive results of clinical trials, it is currently recommended for migraine prevention. However, the mechanism responsible for such protective action remains unknown. Parthenolide, a major ingredient of feverfew, is a reactive molecule that can interact with nucleophilic sites of transient receptor potential ankyrin 1 (TRPA1). Thus, we hypothesized that parthenolide inhibits TRPA1 channel on peptidergic trigeminal nerves.

Patients (or Materials) and Methods: Experiments were performed in vitro in human and mouse cultured cells/neurons and rat isolated tissues, and in vivo in rats and wild-type and TRPA1-deficient mice. Electrophysiologic, calcium, neuropeptide release, smooth muscle motility, allodynic and nociceptive responses, and changes in meningeal blood flow were evaluated.

Results: Parthenolide selectively activates recombinant (transfected cells) or natively expressed (rat/mouse trigeminal neurons) TRPA1, and, by targeting TRPA1, activates trigeminal nerve endings. However, parthenolide behaves as a partial agonist at neuronal TRPA1 of the rat urinary bladder, desensitizes the recombinant TRPA1, and, after initial stimulation, renders peptidergic, TRPA1-expressing nerve terminals unresponsive to any stimulus. These effects causes abrogation of nociceptive responses evoked by TRPA1 agonists, and inhibition of calcitonin gene-related peptide (CGRP) release from trigeminal neurons, and, in particular, of CGRP-mediated

meningeal vasodilatation evoked by TRPA1 stimulants and other mechanisms.

Conclusion: Peculiar features of parthenolide (TRPA1 partial agonism, channel desensitization, and defunctionalisation of peptidergic primary sensory neurons), ultimately resulting in the inhibition of CGRP release from trigeminal neurons, may contribute to the anti-migraine effect of feverfew.

Disclosure of Interest: None declared.

PP273—EFFECT OF THE GABAA LIGANDS CLOBAZAM AND CLONAZEPAM ON THE MODULATION OF PAIN TRANSMISSION IN HUMANS: A PK-PD STUDY

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Introduction: Facilitation of spinal GABAergic inhibition with benzodiazepines (BZD) reverses pain sensitization in rodents. In human, the use of BZD in pain is limited by their sedative effect. We previously demonstrated the antihyperalgesic effect of clobazam, a 1,5-BZD, in mice and its lack of sedation at effective doses. Hence we designed a pharmacokinetic-pharmacodynamic study to explore the effect of antihyperalgesic effect of BZD in healthy volunteers.

Patients (or Materials) and Methods: Randomized, double-blind, crossover controlled study in 25 healthy volunteers comparing clobazam 20 mg with clonazepam 1 mg (positive control) and tolterodine 1.37 mg (active placebo) 2 weeks apart. The primary outcome was the effect on the size of secondary hyperalgesia elicited by the UVB irradiation of the skin of the forearm (sunburn model). Quantitative sensory testing, nociceptive flexion reflex, and the cold pressor test were also performed. Sedation was measured by a visual analog scale (VAS), the digit substitution symbol test (DSST), and saccadic eye movements (SEM) recording. Blood samples were taken to determine the pharmacokinetic of clobazam.

Results: We observed a reduction of the area of the secondary hyperalgesia with clobazam and clonazepam. The maximum of the effect was seen at $t = 2$ hours (median of the difference between $t = 2$ and baseline [MOD2-0] [\pm CI] vs placebo: 19.2 cm² (-2.7-37.9) $P = 0.07$ for clobazam and 29.6 cm² (2.0-55.1), $P = 0.03$, for clonazepam), in line with the expected T_{max} of the compounds. Regarding sedation, at $t = 2$ hours, we saw an effect of the 2 active compounds on the VAS (MOD2-0 [\pm CI] vs placebo: 14 mm (1.0-21.5), $P = 0.03$ for clobazam and 26 mm (14.0-37.5), $P < 0.001$ for clonazepam) and on the peak velocity of the SEM (MOD2-0 [\pm CI] vs placebo: 30.8 deg./s. (6.6-60.6), $P < 0.01$ for clobazam and 55.2 deg./s. (24.5-85.0), $P < 0.01$ for clonazepam). The DSST was only impaired by clonazepam (MOD2-0 [\pm CI] vs placebo: 11.0 (5.0-18.0), $P = 0.03$). These effects disappeared at $t = 8$ hours except that clonazepam still impaired SEM (median of the difference between $t = 8$ and baseline [\pm CI] vs placebo: 28.3 deg./s. (5.3-52.7), $P = 0.01$).

Conclusion: Clobazam and clonazepam decreased the area of secondary hyperalgesia in the sunburn model, which suggests that GABAA receptor ligands are involved in the modulation of pain sensitization in human. Clobazam was less sedative than clonazepam and therefore a suitable "tool compound" to assess the role of GABAergic pathways in human.

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